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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,820	06/05/2001	Giuseppe Locatelli	1303-122	9636

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/25/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,820	LOCATELLI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 17* is/are rejected.

7)☒ Claim(s) *4-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-17 and species III (HHV-8) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that there is a special technical feature linking the claims. This is not found persuasive for several reasons. First, Applicant's entire argument relating to the calibrator as it is claimed in claim 18 is not relevant to the claim. Applicant argues that the specification teaches a product which is different than the prior art. However, this argument is entirely irrelevant since limitations from the specification are not read into the claims. So to the extent that the specification may encompass features not taught by the prior art, these features are not in the claims and do not prevent proper lack of unity. Second, Applicant argues that the reference is unsupported regarding the lack of unity analysis. This is not correct as a well reasoned statement by the European examiner explains why the invention lacks inventive step. Finally, Applicant argues that Gibson does not teach maintaining the same nucleotide composition. This argument is not correct since Gibson expressly teaches scrambling of the internal sequence (see page 995, column 1).

The requirement is still deemed proper and is therefore made FINAL.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences in the claims or in the specification are not

properly identified by SEQ ID NO. Correction is required and failure to correct will be deemed nonresponsive. It is noted that the CRF is fine and computer searching of this case was performed.

Claim Rejections - 35 USC § 101

2. Claim 17 provides for the use of a calibrator, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 17 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Objections

3. Claims 4-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-17 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

4. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase in claim 1 "with the exception of one region which in the target nucleic acid hybridizes with a probe labeled with a reporter and a quencher, that region of the calibrator" is vague and indefinite because the prhase is entirely unclear. For example, is the region of the target nucleic acid the same as the region in the calibrator, is it different, is it adjacent to the region which is corresponding to the calibrator, or is some other meaning intended. This limitation is extremely unclear.

In claim 2, the phrase "with the exception of those regions which in the target nucleic acid hybridize with a probe labeled with a reporter and a quencher and additionally hybridizing with two or more primers, said regions having each other the same nucleotide composition, but with random sequence and a similar Tm" is vague and indefinite. For example, it is simply completely unclear what is meant by "said regions having each other the same nucleotide composition". What limitation is intended by this phrase? Are the nucleotide compositions supposed to switch off between regions or be identical or some palindrome or what. What is supposed to have a similar Tm? The entire limitation is unclear.

With regard to the word "random", in claim 1 or 2, this word is interpreted broadly as referring to any altered sequence which meets the structural requirements imposed by the claim, since no specific sequence information is conveyed by the word "random".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al (Genome Research (1996) 6:995-1001) in view of WalkerPeach et al (U.S. 6,395,470).

Gibson teaches a method for the quantitative detection of a nucleic acid target from a sample (abstract), comprising the steps:

(a) extraction of the target nucleic acid from the sample (page 1000, column 2, subheading "RNA extraction")

(b) mixing under conditions suitable for a polymerization reaction (page 1000, column 2, subheading "QC RT-PCR") (Gibson expressly teaches that "Assay throughput could be increased by adding both probes to the same RT-PCR tube (page 999, column 1)".)

(i) the extracted target nucleic acid and calibrator (ie internal control) where the calibrator (internal control) can be designed by "scrambling of

the internal sequence" (see page 995, column 1) and where the calibrator should "contain similar guanine + cytosine (G+C) content and be of equal or similar length" (see page 995, column 1) (for mixing see page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1)

(ii) forward and reverse primers which anneal to regions on both the target and calibrator nucleic acids, (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1) ,

(iii) probes that are doubly labeled with reporter and quencher fluorophores that hybridize to the target nucleic acid and the calibrator (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1)

(iv) a nucleic acid polymerase with a 5'-3' nuclease activity (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1)

(c) determination of the signal associated with the reporters released due to the 5' polymerase nuclease activity (page 998, figure 3).

Gibson does not teach addition of the calibrator prior to the extraction procedure. Gibson does not expressly teach that the Tm should be kept as identical as possible.

WalkerPeach teaches a method of using an internal control to monitor nucleic acid amplification assays (see column 1, lines 50-65) where the internal control can be added either before or after extraction (see column 14, lines 30-32). WalkerPeach teaches that the internal control will have the identical sequence in an inverted orientation to create a control sequence which will have identical nucleotide composition with the sample and identical Tm (see column 5, lines 21-26). In particular,

WalkerPeach teaches "The present invention allows an investigator to control for inhibition of a sequence amplification reaction with a control sequence that has the same Tm as the target sample (column 5, lines 62-64)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the internal control of WalkerPeach in the method of Gibson since WalkerPeach notes "This quantitative sequence similarity between target and control ICC sequences provides a number of advantages over conventional methods. For example, since the amplified sequences of the target and control plasmids are of the same length and composed of the same nucleotide bases, the reaction parameters for the two plasmids are identical. Reaction parameters such as the Tm, the length of the sequence amplified, primer annealing or hybridization and primer usage are all substantially the same for the experimental and control sequences of the present invention. Given the similarity in reaction parameters between the two sequences, the yield of the co-amplification reactions should also be similar. Thus the inverted sequence of the control plasmid provides an extremely valid method for investigators to monitor for inhibition during signal amplification reactions. (see column 5, lines 46-60)". Further, WalkerPeach expressly motivates the use of this internal control into a broad range of amplification assays, noting "The present invention contemplates utility for use as an internal inhibition control in a variety of signal amplification assays. Examples of signal amplification assays include: the polymerase chain reaction (PCR), variations of PCR, including reverse transcriptase PCR, real-time PCR, branched DNA (bDNA) assays, nucleic acid sequence based amplification assays (NASBA), transcription

mediated amplification (TMA), cytoflowmetric assays, molecular beacon assays, hydridization reactions, and detection assays (see column 4, lines 10-18)".

An ordinary practitioner would have been motivated to modify the method of Gibson to use the internal control of WalkerPeach for the expressly identified advantages of providing an extremely valid method which minimizes variation in reaction parameters. Further, an ordinary practitioner would have been motivated to follow the express guidance of WalkerPeach in adding the internal control before extraction in order to accurately assess the amount of nucleic acid present prior to extraction.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

November 19, 2002